REMARKS

Claim 9 has been amended to include the limitation "over a period of at least 13 weeks". This amendment is supported by the following description on page 28, lines 10 to 16 of the Substitute Specification filed November 16, 2001 (hereafter simply referred to as "the Substitute Specification":

> In the recipient mice given a radiation dose of 6.5 Gy, the skin graft was rejected in one of 7 mice in the intravenous administration group at week 3 after transplantation but successful engraftment was obtained in 3 of the 3 recipient mice in the portal administration group at week 13 after transplantation.

On page 2 of the Advisory Action, the Examiner maintains the rejection of Claims 9-10 under 35 U.S.C. § 103 as being unpatentable over Slavin et al in view of Ildstat et al, Zhang et al and Sachs.

The Examiner acknowledges that TBI taught in Slavin et al was conducted at a dose of 4.0 Gy, which is much less than claimed in the present application. However, it is the Examiner's position that one skilled in the art would appreciate that a higher dose of TBI might be beneficial as taught by Sachs (*sic* Ildstad et al). Thus, the Examiner contends that the present invention would have easily been achieved by combining Slavin et al, which discloses TLI and TBI, and also discloses performing TLI and administration of bone marrow cells (BMC) within one day, with Ildstad et al which teaches TBI of higher values.

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

The Examiner contends that Figs. 5, 7, 17 and 20, and Tables 1-3 of Slavin et al teach that an engraftment rate of

100% is achieved. Applicants respectfully submit that the Examiner is in error.

In the present invention, the establishment of immunological tolerance at the time of organ transplantation was evaluated using as an indicator, the engraftment rate of skin grafts, which are most susceptible to rejection (see page 23, bottom line to page 24, line 4 of the Substitute Specification).

In contrast, Figs. 5, 7 and 20 of Slavin et al merely show the results for bone marrow cells (BMC), spleen cells, and the like, and do not describe the results of organ grafts.

Thus, a person skilled in the art could not predict from Figs. 5, 7, 20 of Slavin et al that organ grafts according to the present invention would achieve an engraftment rate of 100%. (The details of Fig. 5 are described in Example 10 in column 34 of Slavin et al, the details of Fig. 7 are described in Example 11 in column 36 of Slavin et al, and the details of Fig. 20 are described in Example 15 in column 40 of Slavin et al).

Fig. 17 of Slavin et al shows BM stromal grafts and heart grafts, but the results show that "100% of the BM stromal grafts and approximately 80% of the heart grafts survived" (as described in Example 14 in column 39 of Slavin et al). That is, the heart grafts clearly do not achieve an engraftment rate of 100%. Furthermore, Slavin et al does not describe the graft survival period.

Thus, a person skilled in the art could not predict from the results of Fig. 17 of Slavin et al whether or not organ grafts according to the present invention would achieve an engraftment rate of 100%, much less over a period of at least 13 weeks, as claimed.

Slavin et al describes in column 2, lines 29-34 that "Unfortunately, consistent induction of chimerism using TLI has required very high cumulative dose of irradiation (3,400-4,400 cGy) that again would not be desirable for transplant recipients" and "TLI has significant advantages over TBI". Slavin et al further describes in column 2, lines 39-43 that "long courses of TLI can be time consuming and may be associated with short and long-term side effects that may not be suitable for routine clinical application". Further, Slavin et al describes in column 3, lines 5-8 that "It is particularly advantageous to use a short course of TLI (sTLI) as the immunosuppressive agent, for example, 1-12, frequently 1-6, doses of 200 cGy/dose."

Slavin et al mentions skin grafts of 6, 8, 12 and 17 fractions of TLI in Example 2 and Table 1 (columns 26-27). More specifically, Slavin et al describes on lines 2-4 of column 26 that "A short course of TLI (sTLI), in contrast to a long course of TLI (17 fractions, 200 cGY each), was insufficient for acceptance of stem cells from allogeneic BMC or blood.", and further describes on lines 12-14 of the same column that "Thus, after sTLI alone, sufficient numbers of immunocompetent cells remain in the host to reject a donor allograft."

These descriptions indicate that even though sTLI is preferable to TBI and long course of TLI, good skin grafts can not be achieved by sTLI alone.

Thus, a person skilled in the art would not foresee from Table 1 of Slavin et al that organ grafts according to the present invention could achieve an engraftment rate of 100%.

Tables 2 and 3 of Slavin et al show the results of skin grafts performed using an immunosuppressant Cy together with sTLI, based on the results of Table 1. The donor cell used in the present invention is a non T cell depleted BMC. Of the donor cells shown in Tables 2 and 3, Nos. 1-4 in Table 2 and Nos. 1-3 in Table 3 are non-T cell depleted induced graft versus host disease (GVHD).

Thus, a person skilled in the art would not foresee from Tables 2 and 3 of Slavin et al that organ grafts according to the present invention could achieve an engraftment rate of 100%.

Moreover, Slavin et al teaches that TBI is less preferred to TLI (see column 8, lines 63-65). Further, with reference to Figure 2 thereof, it is apparent that merely adjusting the dose of irradiation does not improve both survival % and SKIN ACCEPTANCE % (see Figure 2 of Slavin et al; and EXAMPLE 9 from column 32, line 11 to column 34, line 50 thereof). Specifically, Figure 2 of Slavin et al shows that survival % activity actually decreases as the dose of irradiation increases.

Thus, in view of Figure 2 of Slavin et al, wherein increasing the dose of irradiation reduces survival %, a person skilled in the art would never think of increasing the dose of TBI in the method of Slavin et al.

Hence, one skilled in the art would not have been motivated, based on the teachings in Slavin et al to combine Slavin et al with Ildstad et al to use a dose of 6.5 Gy, as claimed in the present application. That is, one skilled in the art would have considered it undesirable to combine TBI with irradiation at values higher than 4.0 Gy, as based on

Slavin et al, one skilled in the art would have considered such high values would have reduced survival %.

The Examiner contends that Fig. 7 of Ildstad et al. teaches bone marrow engraftment after sublethal total body irradiation is reliably achieved in 100% of recipients at 7.0 Gy. Applicants respectfully submit that the Examiner is in error.

Fig. 7 of Ildstad et al. shows that donor-type skin grafts achieved an engraftment rate of 100% until day 19, but thereafter the engraftment rate fell to about 90% (see ■: DONER-SPECIFIC in Fig. 7 of Ildstad et al). More specifically, in Ildstad et al, an engraftment rate of 100% was not achieved beyond day 19.

Thus, the technique of Ildstad et al is clearly different from the subject matter of the present invention as recited in amended Claim 9.

That is, with respect to "an engraftment rate of 100%", Applicants submit that the insertion of the phrase "over a period of at least 13 weeks" into Claim 9 clearly distinguishes the present invention from the combination of Slavin et al and Ildstad et al. Intravenous administration as taught in Ildstad et al may temporally induce immunological tolerance, but a long-term and sufficient immunological tolerance is not achieved (see, for example, Fig. 7 of Ildstad et al: an engraftment rate of 100% cannot achieved beyond day 19).

As explained above, Slavin et al principally discloses a method for inducing immunotolerance using sTLI.

As shown above, Slavin et al teaches the following:

"Unfortunately, consistent induction of chimerism using TLI has required very high cumulative dose of irradiation

(3,400-4,400 cGy) that again would not be desirable for transplant recipients." (column 2, lines 29-34);

"long courses of TLI can be time consuming and may be associated with short and long-term side effects that may not be suitable for routine clinical application" (column 2, lines 39-43); and

"It is particularly advantageous to use a short course of TLI (sTLI) as the immunosuppressive agent, for example, 1-12, frequently 1-6, doses of 200 cGy/dose." (column 3, lines 5-8).

Fig. 2 of Slavin et al teaches that even when using TLI, a high dose level of irradiation results in a high recipient mortality rate.

Slavin et al further describes the following:

"TLI has significant advantages over TBI" (column 2, lines 32-34); and

"Due to its non-selective effects on all of the host's hematopoietic cells ant its severe immediate and long-term side effects, TBI is not preferred." (column 8, lines 63-65).

Thus, Slavin et al teaches that TBI is less preferable than TLI.

Slavin et al further teaches that when using TBI, it should be performed at a low radiation dose level. More specifically, Slavin et al describes the following:

"If TBI is used, it should be at a dose level that causes no severe or irreversible pancytopenia" (column 8, lines 65-57).

Slavin et al gives 4.0 Gy of TBI as an example of such a radiation dose (column 23, line 40, and column 34, line 58).

Therefore, a person skilled in the art could not foresee from the disclosure of Slavin et al that high levels of

irradiation, in particular, high doses of TBI, would achieve better effects than those disclosed in Slavin et al.

In this regard, Ildstad et al discloses about 7.0 Gy of TBI. That is, Ildstad et al discloses a high dose level for TBI, which is not preferable according to Slavin et al.

Thus, a person skilled in the art would not have been motivated to combine Slavin et al's technique with Ildstad et al's technique. Even if these techniques were combined, a person skilled in the art would expect that using a high dose level of TBI as taught in Ildstad et al in the method of Slavin et al would merely achieve a worse effect than that disclosed in Slavin et al.

Sachs et al discloses 4.0 Gy of TBI and describes TBI and bone marrow cell administration performed on the same day. The 4.0 Gy of TBI disclosed in Sachs et al is the same as disclosed in Slavin et al. Thus, a person skilled in the art combining Slavin et al's technique with Sach et al's technique would expect only the same level of effects as achieved by Slavin et al.

In fact, even 6.0 Gy of TBI does not achieve an engraftment rate of 100%, as described in Test Example 4 on page 28, lines 5-10 of the Substitute Specification. Thus combining Sachs et al's technique with Slavin et al's technique, TBI with a radiation dose of 4.0 Gy, cannot achieve the excellent effect of the present invention due to the insufficient level of radiation.

Zhang et al describes the effects of intravenous and portal venous administrations of bone marrow cells on prolonged graft survival. Fig. 4 of Zhang et al shows that bone marrow cells administered by portal venous injection are accumulated in the

liver at higher levels than by intravenous injection, and thus indicates that portal venous administration might provide a higher immunological tolerance-inducing effect than intravenous administration

However, even if Slavin et al's technique was combined with Zhang et al's technique, a person skilled in the art could neither predict therefrom whether the excellent immunological tolerance-inducing effect as achieved by the present invention could be achieved, nor foresee how irradiation before portal venous administration could affect immunological tolerance-inducing effects.

As is clear from the above, a person skilled in the art would not have been motivated to combine Slavin et al, Ildstad et al, Sach et al and Zhang et al to provide an excellent immunological tolerance-inducing effect. Even if these techniques were combined, a person skilled in the art could not foresee therefrom that the excellent immunological tolerance-inducing effect as achieved by the present invention could be achieved.

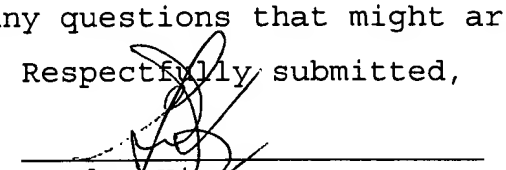
Based on the teaching of Slavin et al, a person skilled in the art would rather expect that a combination of Slavin et al, Ildstad et al, Sach et al and Zhang et al would achieve a lower effect than that disclosed in Slavin et al.

Accordingly, Applicants respectfully submit that the present invention is not taught or suggested by Slavin et al alone or when combined with the teachings of Ildstad et al and Zhang et al, and Sachs et al and in any event, such a combination can only be made in hindsight, which is legally improper. Thus, Applicants request withdrawal of the Examiner's rejection.

In view of the amendments to the claims and arguments set forth above, reexamination, reconsideration and allowance are respectfully requested.

The Examiner is invited to contact the undersigned at the telephone number listed below on any questions that might arise.

Respectfully submitted,



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